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Amendments to the Specification

Please insert the following paragraph prior to the first sentence of the application (p. 1, between lines 2 and 3):

--CROSS REFERENCE TO RELATED APPLICATIONS

This application is a 35 U.S.C. §371 U.S. national phase application of International Application PCT/US99/04326, filed February 26, 1999, which claims priority to U.S. Provisional Application Ser. No. 60/076,565, filed March 2, 1998, both of which are hereby incorporated by reference in their entireties.--

Please replace the paragraph bridging p. 1 to p. 3, with the following paragraph:

--An immunogenic species-common protein has been identified from *Streptococcus pneumoniae* (Russell et al. 1990, "Monoclonal antibody recognizing a species-specific protein from *Streptococcus pneumoniae*," J. Clin. Microbiol. 28: 2191-2195; and U.S. Patent No. 5,422,427). A 37-kDa *S. pneumoniae* protein has been the focus of several studies and is now designated pneumococcal surface adhesin protein A (PsaA). (This 37-kDa protein was referred to as pneumococcal fimbrial protein A in U.S. Patent No. 5,422,427; the terms are used interchangeably in the present specification.) Immunoblot analysis studies using anti-PsaA monoclonal antibody showed that PsaA is common to all 23 pneumococcal vaccine serotypes (Russell et al. 1990). Enzyme-linked-immunosorbent assay studies have indicated that patients with pneumococcal disease show an antibody increase in convalescent-phase serum to PsaA compared with acute-phase serum antibody levels (Tharpe et al. 1995, "Purification and seroreactivity of pneumococcal surface adhesin A (PsaA)," Clin. Diagn. Lab. Immunol. 3:227-229; and Tharpe et al. 1994, "The utility of a recombinant protein in an enzyme immunoassay for antibodies against *Streptococcus pneumoniae*," Abstr. V-2, p 617. 1994. American Society for Microbiology, Washington, D.C.). Additionally, a

limited *in vivo* protection study showed that antibodies to the 37-kDa protein protect mice from lethal challenge (*Talkington et al.* 1996, "Protection of mice against fatal pneumococcal challenge by immunization with pneumococcal surface adhesin A (PsaA)," *Microbial Pathogenesis* 21:17-22). The gene encoding PsaA from *S. pneumoniae* strain R36A (an unencapsulated strain) has been cloned in *Escherichia coli* and sequenced, but this strain does not contain a 37-kDa protein encoding nucleic acid that is highly conserved among the various serotypes. (*Sampson et al.* 1994, "Cloning and nucleotide sequence analysis of *psaA*, the *Streptococcus pneumoniae* gene encoding a 37-kilodalton protein homologous to previously reported *Streptococcus* sp. adhesins," *Infect. Immun.* 62:319-324). This particular nucleic acid and the corresponding polypeptide, therefore, are of limited value for use as diagnostic reagents, in preventing infection, in treating infection, or in vaccine development. In United States Patent Application Serial No. 08/715,131, filed Sept. 17, 1996, (now U.S. Patent No. 5,854,416) which is a continuation-in-part of United States Patent Application Serial No. 08/222,179, filed April 4, 1994, which is a continuation-in-part of United States Patent Application Serial No. 07/791,377, filed September 17, 1991 (now U.S. Patent No. 5,422,427), all of which are hereby incorporated by reference in their entirety, an isolated nucleic acid encoding the 37-kDa protein of *Streptococcus pneumoniae*, unique fragments of at least 10 nucleotides of this nucleic acid which can be used in methods to detect the presence of *Streptococcus pneumoniae* in a sample and as immunogenic vaccines have been disclosed. Furthermore, a purified polypeptide encoded by this nucleic acid, encoding the 37-kDa protein of *Streptococcus pneumoniae*, which can be used in immunogenic vaccines, has been disclosed. Additionally, purified antibodies which bind to the 37-kDa protein of *Streptococcus pneumoniae* or fragments thereof, which can be used in methods to detect the presence of *Streptococcus pneumoniae*, and in therapeutic and prophylactic methods, have been disclosed. Sequence

conservation is a necessary requirement for a candidate species-common vaccine. The sequence conservation of the *psaA* gene among pneumococcal types, and specifically among encapsulated pneumococci which cause the vast majority of cases of serious disease, remains under investigation. There exists a need to identify characteristic epitopes related to *S. pneumoniae* PsaA in order to provide polypeptides which can serve as a vaccine for multiple strains of *Streptococcus pneumoniae*. The present invention addresses this need by determining effective epitopic peptides related to *S. pneumoniae* PsaA, and employing those peptides in therapeutic compositions directed against *Streptococcus pneumoniae* infection.--

Please replace the paragraph bridging p. 7 to p. 8, with the following paragraph:

--In one aspect, the invention provides an isolated nucleic acid encoding the 37-kDa protein of *Streptococcus pneumoniae* whose amino acid sequence is set forth in the Sequence Listing as SEQ ID NO:2. The term "isolated" refers to a nucleic acid which is essentially separated from other genes that naturally occur in *S. pneumoniae*. In one embodiment, the present invention provides an isolated nucleic acid encoding the 37-kDa protein of *Streptococcus pneumoniae* wherein the nucleic acid is the nucleic acid whose nucleotide sequence is set forth in the Sequence Listing as SEQ ID NO:1. An isolated nucleic acid comprising a unique fragment of at least 10 nucleotides of the nucleic acid set forth in the Sequence Listing as SEQ ID NO:1 is also provided. "Unique fragments," as used herein, means a nucleic acid of at least 10 nucleotides that is not identical to any other known nucleic acid sequence at the time the invention was made. Examples of the sequences of at least 10 nucleotides that are unique to the nucleic acid set forth in the Sequence Listing as SEQ ID NO: 1 can be readily ascertained by comparing the sequence of the nucleic acid in question to sequences catalogued in GenBank®, or other sequence database, using computer programs such as DNASIS® (Hitachi Engineering, Inc.), or Word Search or FASTA of the Genetics Computer Group

(GCG) (Madison, WI), which search the catalogued nucleotide sequences for similarities to the nucleic acid in question. If the sequence does not match any of the known sequences, it is unique. For example, the sequence of nucleotides 1-10 can be used to search the databases for an identical match. If no matches are found, then nucleotides 1-10 represent a unique fragment. Next, the sequence of nucleotides 2-11 can be used to search the databases, then the sequence of nucleotides 3-12, and so on up to nucleotides 1321 to 1330 of the sequence set forth in the Sequence Listing as SEQ ID NO:1. The same type of search can be performed for sequences of 11 nucleotides, 12 nucleotides, 13 nucleotides, etc. The possible fragments range from 10 nucleotides in length to 1 nucleotide less than the sequence set forth in the Sequence Listing as SEQ ID NO:1. These unique nucleic acids, as well as degenerate nucleic acids can be used, for example, as primers for amplifying nucleic acids from other strains of *Streptococcus pneumoniae* in order to isolate allelic variants of the 37-kDa protein, or as primers for reverse transcription of 37-kDa protein RNA, or as probes for use in detection techniques such as nucleic acid hybridization. One skilled in the art will appreciate that even though a nucleic acid of at least 10 nucleotides is unique to a specific gene, that nucleic acid fragment can still hybridize to many other nucleic acids and therefore be used in techniques such as amplification and nucleic acid detection.--

Please replace the paragraph bridging p. 9 to p. 10, with the following paragraph:

--Unique fragments of the 37-kDa protein can be identified in the same manner as that used to identify unique nucleic acids. For example, a sequence of 3 amino acids or more, derived from the sequence of the 37-kDa protein, as set forth in the Sequence Listing as SEQ ID NO:2, can be used to search the protein sequence databases. Those that do not match a known sequence are therefore unique. Methods of preparing these proteins and protein fragments are set forth in United States Patent Application Serial No. 08/715,131, filed Sept. 17, 1996 (now U.S. Patent No.

5,854,416), which is a continuation-in-part of United States Patent Application Serial No.

08/222,179, filed April 4, 1994, which is a continuation-in-part of United States Patent Application Serial No. 07/791,377, filed September 17, 1991 (now U.S. Patent No. 5,422,427).--

Please replace the paragraph on page 12, lines 8-19, with the following paragraph:

--The monoclonal antibodies (MAbs) employed in the present invention (disclosed in United States Patent Application Serial No. 08/715,131, filed Sept. 17, 1996 (now U.S. Patent No. 5,854,416), incorporated herein by reference) are MAb 1E7A3D7C2, or a fragment thereof which retains the characteristics of antibody 1E7A3D7C2, such as its binding specificity and its binding affinity; MAb 1B6E12H9, or a fragment thereof which retains the characteristics of antibody 1B6E12H9; MAb 3C4D5C7, or a fragment thereof which retains the characteristics of antibody 3C4D5C7; MAb 4E9G9D3, or a fragment thereof which retains the characteristics of antibody 4E9G9D3; MAb 4H5C10F3, or a fragment thereof which retains the characteristics of antibody 4H5C10F3; MAb 6F6F9C8, or a fragment thereof which retains the characteristics of antibody 6F6F9C8; and MAb 8G12G11B10, or a fragment thereof which retains the characteristics of antibody 8G12G11B10.--

Please replace the paragraph on page 12, lines 20-25, with the following paragraph:

--The hybridomas used to produce the respective monoclonal antibodies employed in the present invention (disclosed in United States Patent Application Serial No. 08/715,131, filed Sept. 17, 1996 (now U.S. Patent No. 5,854,416), incorporated herein by reference) are hybridoma 1E7A3D7C2, hybridoma 1B6E12H9, hybridoma 3C4D5C7, hybridoma 4E9G9D3, hybridoma 4H5C10F3, hybridoma 6F6F9C8, and hybridoma 8G12G11B10.--

Please replace the paragraph on page 24, lines 7-24, with the following paragraph:

--ELISA. Screening of hybridoma culture supernatants was done by ELISA. U-bottom microtitration plates (Costar, Cambridge, Mass.) were sensitized with 50 µl of *S. pneumoniae* whole cell suspension (10^9 CFU/ml) diluted 1:4,000 in 0.1 M carbonate buffer, pH 9.6, and kept for 16 h at 4°C. The plates were washed 5 times with 0.9% NaCl containing 0.05% TWEEN 20 (NaCl-T). Culture supernatants (50 µl) from the fusion plates were added to 50 µl of a solution containing 2% bovine serum albumin (BSA), 10% normal rabbit serum, 0.3% TWEEN-20, and 0.02% Merthiolate in phosphate buffered saline (PBS), pH 7.2, (ELISA diluent; *Wells et al.* (1987) J. Clin. Microbiol. 25:516-521) in the plates and were incubated for 30 min at 37°C. The plates were washed 5 times with NaCl-T. Fifty microliters of goat anti-mouse immunoglobulin horseradish peroxidase conjugate in ELISA diluent was added to each well. The plates were incubated for 30 min at 37°C. The plates were washed, and 50 µl of 3,3',5,5'-tetramethylbenzidine (0.1 mg/ml in 0.1M sodium acetate, 0.1 M citric acid (pH 5.7) with 0.005% hydrogen peroxide) was added to each well and incubated for 30 min at 37°C. The reaction was stopped by adding 1 ml of 4 M H₂SO₄ and the optical density was read on a Dynatech ELISA Reader (Dynatech Laboratories, Inc., Alexandria, Va.) at 450 nm. An optical density of greater than 0.200 was considered positive.--

Please replace the paragraph bridging p. 24 to p. 25, with the following paragraph:

--SDS-PAGE and immunoblot analysis. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was performed by the method of Tsang et al. ((1983) Methods Enzymol. 92:377-391), using an 8% acrylamide resolving gel. Equal volumes of sample buffer (5% SDS-10% 2-mercaptoethanol-20% glycerol in 0.01 M Tris HCl, pH 8.0) and cell suspension containing 2.4 µg protein per µl were mixed, heated at 100°C for 5 min, and a 5-µl sample was applied to 1 of 15 wells. If the final protein content of the portion of sample to be tested was <1.2

µg/µl, a volume up to 10 µl of sample was applied to achieve a final concentration of 6 µl of protein per well. Protein concentrations were determined by the method of Markwell et al. ((1978) Anal. Biochem. 87:206-210), with BSA as the standard. Proteins separated by SDS-PAGE were either silver stained by the method of Morrissey ((1981) Anal. Biochem. 117:307-310) or electro-blotted onto nitrocellulose (Schleicher & Schuell, Inc., Keene, N.H.). The immunoblot procedure was done according to the method of Tsang et al. (1983) with slight modifications. The blots were given three 5-min washes with PBS, pH 7.2, containing 0.3% TWEEN-20 and were gently agitated overnight (16 h) at 25°C. The blots were blocked for 1 h with casein-thimerosal buffer (CTB) (*Kenna et al.* (1985) J. Immunol. Meth. 85:409-419). After three rinses with CTB, the blots were exposed to goat anti-mouse immunoglobulin horseradish peroxidase conjugate (Bio-Rad Laboratories, Richmond, Calif) for 2 h at 25°C. Conjugate dilutions (1:2,000) were made in CTB. The blots were again rinsed three times with CTB and exposed to 3,3'-diaminobenzidine-4-hydrochloride in PBS, pH 7.2 (0.5 mg/ml), with 0.003% H₂O₂ for 5 min at 25°C. Reactivity was expressed as a visible colored band on the nitrocellulose paper. Low molecular-mass protein standards (Bio-Rad Laboratories) were used in PAGE and immunoblotting. Rabbit antisera to the protein standards were used to develop the standards (*Carlone* (1986) Anal. Biochem. 155:89-91). Molecular masses were calculated by the method of Neville et al. ((1974) Methods Enzymol. 32:92-102) using appropriate molecular mass standards.--

Please replace the paragraph bridging p. 25 to p. 26, with the following paragraph:

--Immunoelectron-microscopy. Pneumococcal cells were washed two times with PBS and fixed in a freshly made mixture of 1% paraformaldehyde-0.1% glutaraldehyde for 20 min at 4°C. The cells were dehydrated in a graded alcohol series and then in a 1:1 mixture of absolute ethanol

and LOWICRYL K4M (Ladd Research Industries, Inc., Burlington, Vt.) for 1 h at 4°C. The cells were pelleted and suspended in a 1:2 mixture of absolute ethanol and LOWICRYL K4M for 1 h at 4°C. They were again pelleted and suspended in LOWICRYL K4M (undiluted) for 16 h at 4°C. The cells were transferred to fresh and undiluted LOWICRYL K4M two times during the next 24-hour period. The LOWICRYL K4M-treated cells were imbedded in gelatin capsules and placed in a box lined with aluminum foil. The capsules were hardened using a short-wave UV light source (35 cm distance for 72 h at -20°C). The box was brought to room temperature, and the capsules were allowed to continue hardening for up to 14 days. Samples of the capsule were cut into 100-µm thin sections and picked up on nickel grids. Grids containing the sample were placed on a droplet of ovalbumin solution in PBS containing sodium azide (E.Y. Laboratories, Inc., San Mateo, Calif) for 5 min. The grids (wet) were transferred to a solution of primary MAbs diluted in a solution of BSA reagent (1% BSA in PBS containing 0.1% TRITON X- 100, TWEEN 20, and sodium azide) (E. Y. Laboratories) and incubated for 1 h at room temperature or 18 to 48 h at 4°C in a moist chamber. For antibody binding controls, other grids were wetted with MAbs against *Legionella pneumophila*. The grids were rinsed two times with PBS and incubated on droplets of goat anti-mouse IgG-labeled colloidal gold particles (20 µm)(E. Y. Laboratories) for 1 h at room temperature. The grids were rinsed two times and post-stained with osmium tetroxide, uranyl acetate, and lead citrate. The grids were examined with a Philips 410 transmission electron microscope.--

Please replace the paragraph on page 35, lines 15-19, with the following paragraph:

--(ii) **Enzyme digestion.** Digestion of amplified products was performed as directed by the manufacturer for the designated enzymes in volumes of 20 µl. Digestion products were analyzed by agarose (2% META-PHOR agarose, FMC Corp., Rockland, Me.) gel electrophoresis and visualized after being stained with ethidium bromide.--

Please replace the paragraph bridging p. 36 to p. 38, with the following paragraph:

--Comparison of the serotype 6B sequence with streptococcal homologs. Comparison of the serotype 6B *PsaA* nucleotide sequence (*Bilofsky et al.* 1988. A GENBANK genetic sequence database. Nucleic Acids Res. 16:1861-1864) (GENBANK accession number U53509) and its flanking regions with the previously published strain R36A *psaA* sequence (*Sampson et al.* 1994. "Cloning and nucleotide sequence analysis of *psaA*, the *Streptococcus pneumoniae* gene encoding a 37-kilodalton protein homologous to previously reported *Streptococcus* sp. adhesins." Infect. Immun. 62:319-324) shows the differences between the nucleotide sequences. The computed homology between the two sequences is 74%. Major areas of discord are in regions upstream and downstream of the ORF and in the initial 60 nucleotide which encode the putative signal peptide. When the two *PsaA* coding sequences are compared, the sequence homology increases to 78%. Serotype 6B sequence was also compared to the *psaA* DNA sequence for another vaccine serotype, serotype 2, which was recently submitted to GenBank (Accession number U40786). Computer analysis of these two sequences shows that they are very similar, with computed DNA homology percentages of 99% between the two *psaA* DNA sequences. There are eight single base differences between the two sequences. A comparison of serotype 2 and 6B *PsaAs* shows almost complete identity: the computed similarity value is 99.3. The eight base difference at the nucleotide level translated into a difference at the peptide level of six amino acids with two of the changes resulting in conservative substitutions. Further analyses and comparisons of the serotype 6B sequence to the other five GENBANK *PsaA* homologues from viridans Streptococci and *E. faecalis* (*Fenno et al.* 1989. "Nucleotide sequence analysis of a type I fimbrial gene of *Streptococcus sanguis* FW213." Infect. Immun, 57:3527-3533; *Sampson et al.* 1994. "Cloning and nucleotide sequence analysis of *psaA*, the *Streptococcus pneumoniae* gene encoding a 37-kilodalton protein homologous to

previously reported *Streptococcus* sp. adhesins." Infect. Immun. 62:319-324; *Ganeshkumar et al.* 1991. "Nucleotide sequence of a gene coding for a saliva-binding protein (SsaB) from *Streptococcus sanguis* 12 and possible role of the protein in coaggregation with actinomyces." Infect. Immun. 59:1093-1099; *Kolenbrander et al.* 1994. "Nucleotide sequence of the *Streptococcus gordonii* PK488 coaggregation adhesin gene *scaA* and ATP-binding cassette." Infect. Immun. 62:4469-4480; and *Lowe et al.* 1995. "Cloning of an *Enterococcus faecalis* endocarditis antigen: homology with some adhesins from oral streptococci." Infect. Immun 63:703-706) revealed significant sequence similarity between them. Sequence identities were 81%, 81%, 77%, 82%, and 57%, respectively, for PsaA (*S. pneumoniae* strain R36A), SsaB (*S. sanguis*), FimA (*S. parasanguis*), ScaA (*S. gordonii*) and EfaA (*E. faecalis*). Additionally, all six sequences showed great similarity in organization. They have a hydrophobic leader peptide containing the prolipoprotein consensus sequence LXXC (for signal peptidase II cleavage) within the first 17-20 amino acids. This N-terminal leader sequence appears to represent the area of greatest variability. It is followed by a region of high similarity from amino acids 36 to 150. The region from 150 to 198 is a variable region and is followed by another conserved region (198 to 309).--

Please replace the paragraph bridging p. 38 to p. 39, with the following paragraph:

--The one exception, restriction enzyme *Tsp509I*, had six sites within the gene and generated seven fragments upon digestion with sizes of 7, 30, 68, 146, 151, 166, and 362 bp. When these fragments are separated on 2% META-PHOR agarose gel, a five-band pattern can be seen (7- and 30-bp fragments are not seen on these gels because of their small size). For 21 of 23 serotypes this five-fragment enzyme pattern was obtained; but for strains of serotype 4 and 33F, the 146-bp fragment is absent and two new fragments appear flanking the 68-bp fragment making a total of seven bands. This increase in fragment number results from the presence of an extra *Tsp509I* site

within the 146-bp fragment. To ascertain the prevalence of this extra site, the *Tsp509I* patterns of 3 to 4 additional strains of each of 23 serotype strains (additional strains of serotype 2 and serotype 25 were not available) were analyzed. All strains analyzed were random clinical isolates from the United States that had been submitted to CDC for serotyping. The majority of the 80 strains were blood isolates; exceptions were 2 from cerebrospinal fluid, 2 from pleural fluid, and 1 each from the eye and nose. Of the strains analyzed, 10% had the extra *Tsp509I* site, resulting in the altered RFLP pattern. This modification was seen only in types 4, 8, 11F, and 33F. In an attempt to determine the prevalence of this altered pattern, the *psaA* gene from 8 additional strains of these 4 types was analyzed for the *Tsp509I* variation (bringing the total to 11-12 for these 4 types). Table 1 summarizes the analyses of serotypes 4, 8, 11A, and 33F. The modified pattern is sporadically present in serotypes 4 and 8, but is essentially always present in 11 of 12 strains of 11A and all strains of 33F. The occurrence of this pattern could not be correlated with geographic location or region of the United States since strains that showed variation came from diverse regions of the country. All strains of types 4, 8, 11A, and 33F were blood isolates except one 33F strain, which was a nasal isolate; thus the relevance of the site of isolation on prevalence of this modification could not be assessed.--

Please replace the paragraph on page 40, lines 25-33, with the following paragraph:

--The 37-kDa protein from serotype 22F was used to generate monoclonal antibodies 1B6E12H9, 3C4D5C7, 4E9G9D3, 4H5C10F3, 6F6F9C8, and 8G12G11B10 (disclosed in United States Patent Application Ser. No. 08/715,131 (now U.S. Patent No. 5,854,416), incorporated herein by reference). The MAbs were analyzed for their ability to confer protection from infection by *Streptococcus pneumoniae*. Table 2 shows that of 5 monoclonal antibodies tested, one in particular gave efficient protection from subsequent *S. pneumoniae* challenge (8G12G11B10). The protection

from *S. pneumoniae* was dose-responsive, demonstrating that the monoclonal antibody was responsible for the protection (Table 3).--

Please replace the paragraph bridging p. 42 to p. 43, with the following paragraph:

--High affinity specimens from the library obtained using the procedures of Example 11 were propagated and sequenced. For each MAb, ten phage specimens resulting from the selection process were sequenced. Approximately 1 µg of single-stranded DNA was purified by phenol and chloroform extraction, ethanol precipitated and resuspended in 7 µL water. Sequencing reactions were performed using a 27-mer primer complementary to the FUSE 5 vector sequence derived from a region in wild-type pIII common to all fd-tet derived vectors and ³⁵S SEQUENASE version 2 (U. S. Biochemicals, Cleveland OH). The sequences obtained are shown in Table 4. They were compared to known sequences of PsaA strains 2 and 6B using ClustaIV and tFasta programs to identify the epitope on the PsaA with which each peptide is aligned most closely. These epitope positions are also given in Table 4. The peptide obtained using MAbs 8G12, 6F6, and 1E7 align to PsaA best when an additional residue is present on the protein where the gap appears after residue 13 of the peptide (SEQ ID NO:7 and SEQ ID NO:8).--

Please replace the Abstract with the following paragraph:

--A nucleic acid encoding the 37-kDa pneumococcal surface adhesion A protein (PsaA) from *Streptococcus pneumoniae* and isolated nucleic acids comprising a unique fragment of at least 10 nucleotides of the 37-kDa protein. Also-provided are purified polypeptides encoded by the nucleic acid and the nucleic acids fragment of at least 10 nucleotides. Further provided are monoclonal antibodies which selectively bind PsaA. Peptides are provided that immunospecifically bind to the monoclonal antibodies and are immunogenic against *Streptococcus pneumoniae*. Vaccines comprising such immunogenic polypeptides and methods of conferring protective

immunity against *Streptococcus pneumoniae* infection by administering therapeutic compositions comprising the immunogenic peptides are disclosed. Methods of detecting *Streptococcus pneumoniae* using antibodies or antigens and methods of preventing and treating *Streptococcus pneumoniae* infection are provided. A method of identifying the sequence of a peptide potentially capable of eliciting protective immunity against a pathogenic microorganism is provided.--